

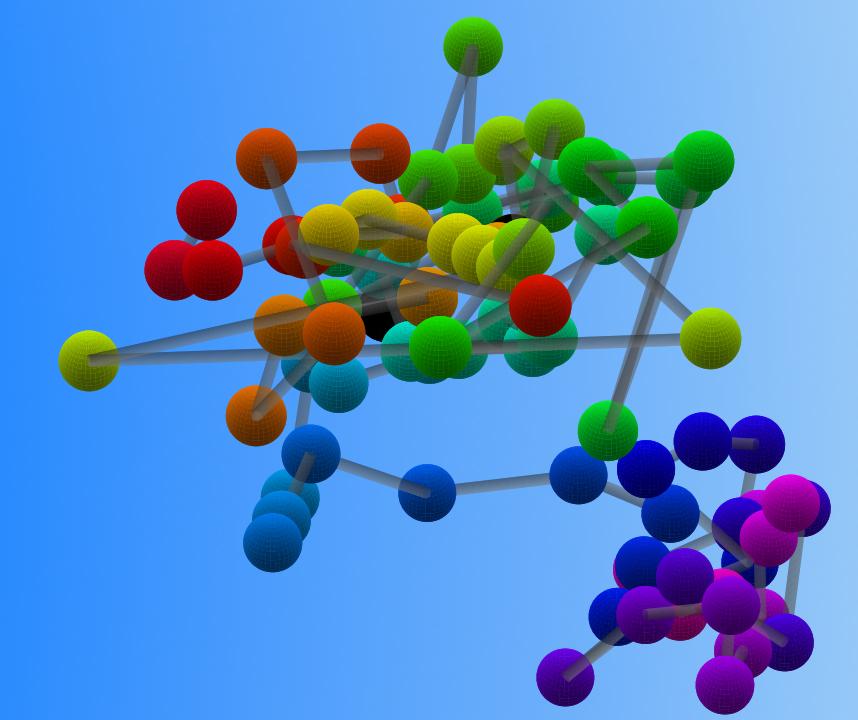
Revealing DNA's topology

A spectral energy approach to loop detection

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Introduction

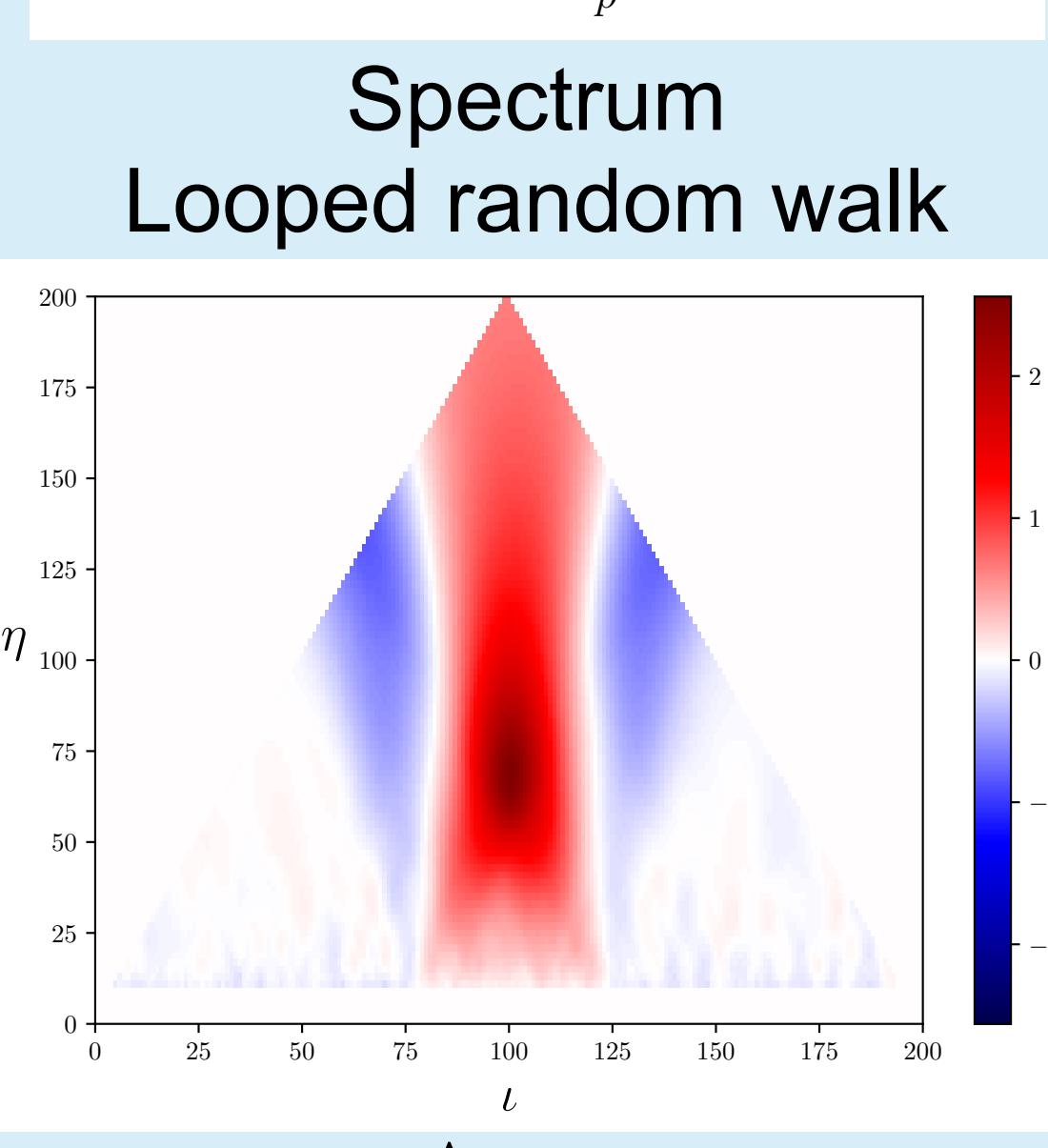
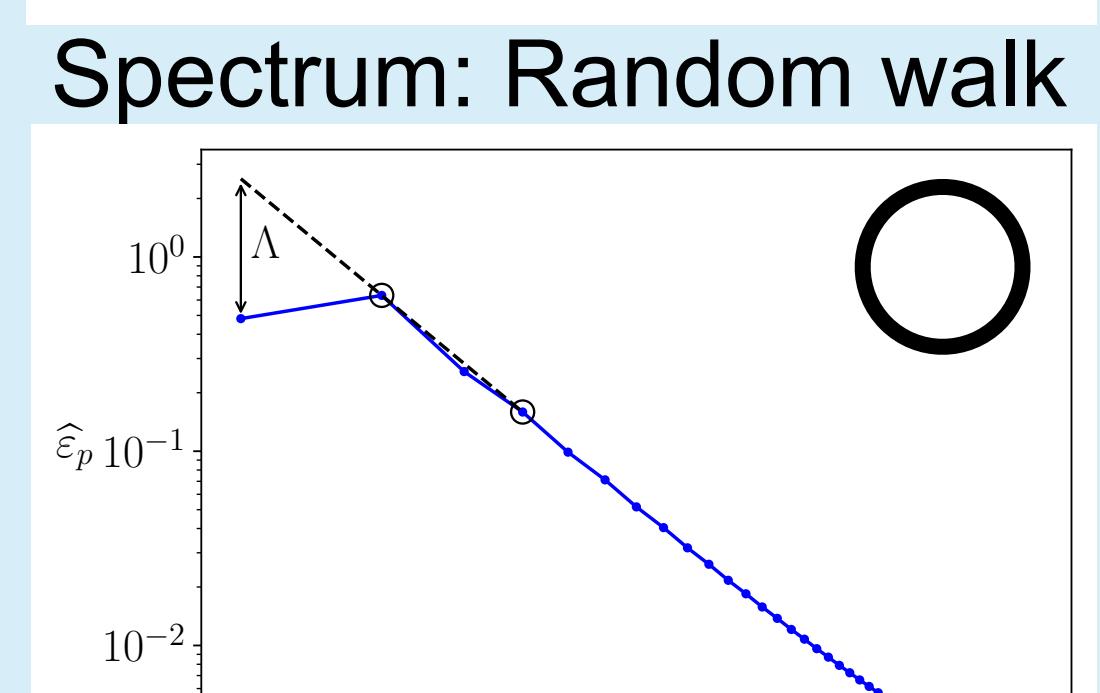
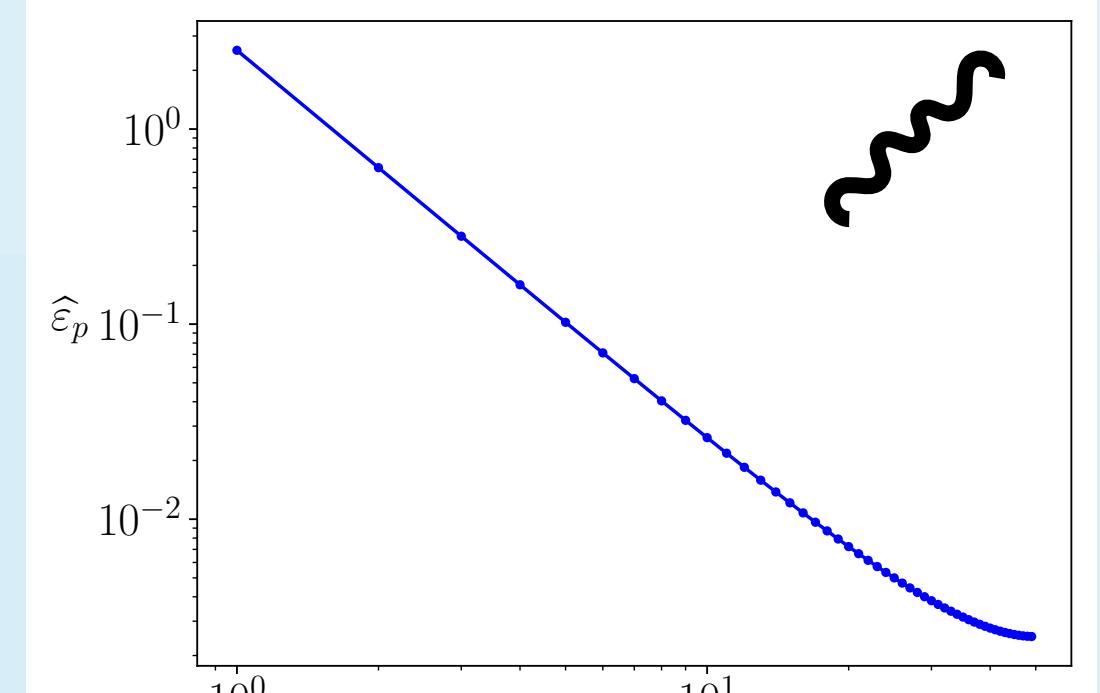
Loops play a central role in the organisation of chromatin and gene regulation:

- Cohesin and CTCF create loops, forming TADs
- Looping DNA initiates transcription through enhancer-promoter proximity

- By revealing the spatial arrangement of chromatin at the single-cell level, sequential FISH imaging allows the study of conformational fluctuations as never before
- Despite unprecedented access to 3D paths, its application in investigating chromatin loops is yet to be fully realised

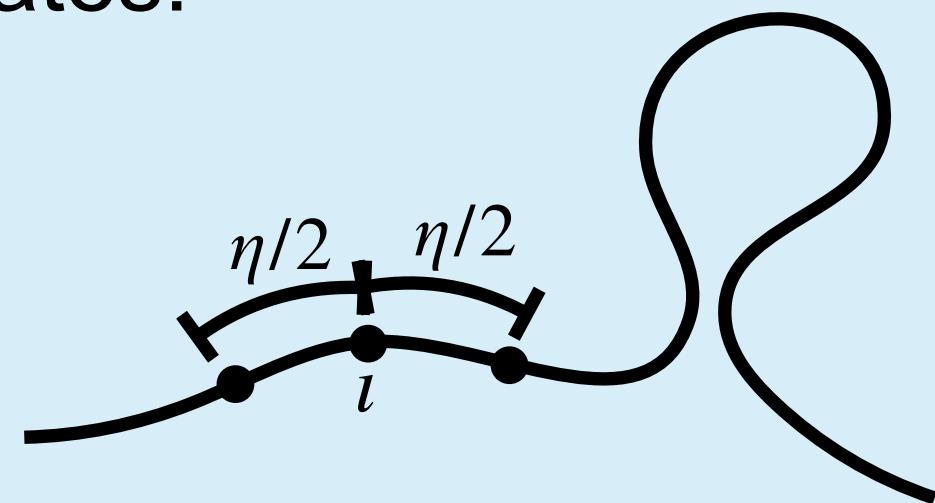
Step 1: Ensemble averages

- Start from 3D-configurations and consider the coordinates as signals
- Calculate the Fourier (cosine) modes of the discrete signals
- Square the modes and average: **spectrum**[2]
- Largest scales (smallest modes) are affected by being looped
- Exploit this: **log-spectral ratio Λ**
- Single number discriminating looped and non-looped
- Apply it to all subchains to get Λ -plot



Λ-plot

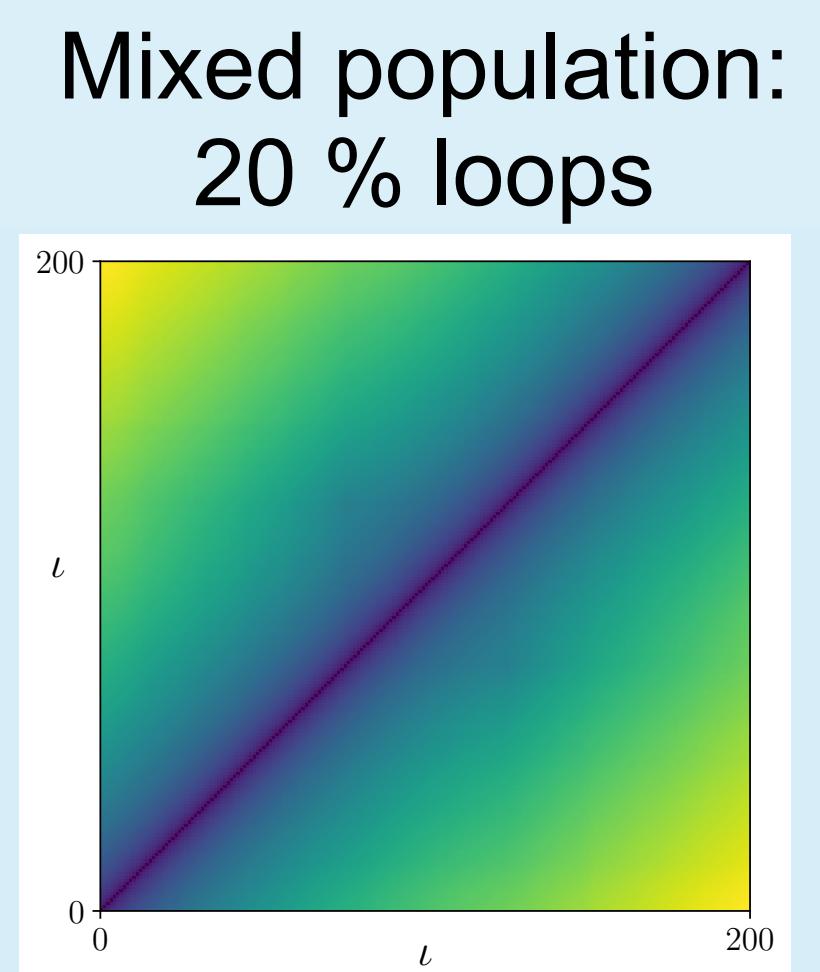
- Coordinates:



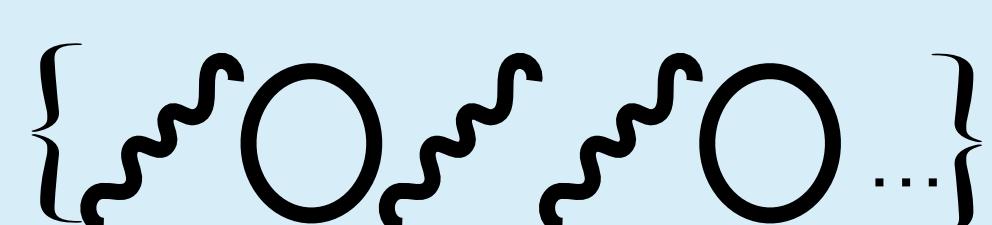
Methods

Step 2: Single cell

- From Λ -plot: know where to look
- Apply Neural network to segregate looped and non-looped confirmations on a single cell level
- Train neural networks on (looped) random walks
- Thanks to Λ -plot, can avoid exponential complexity in training!



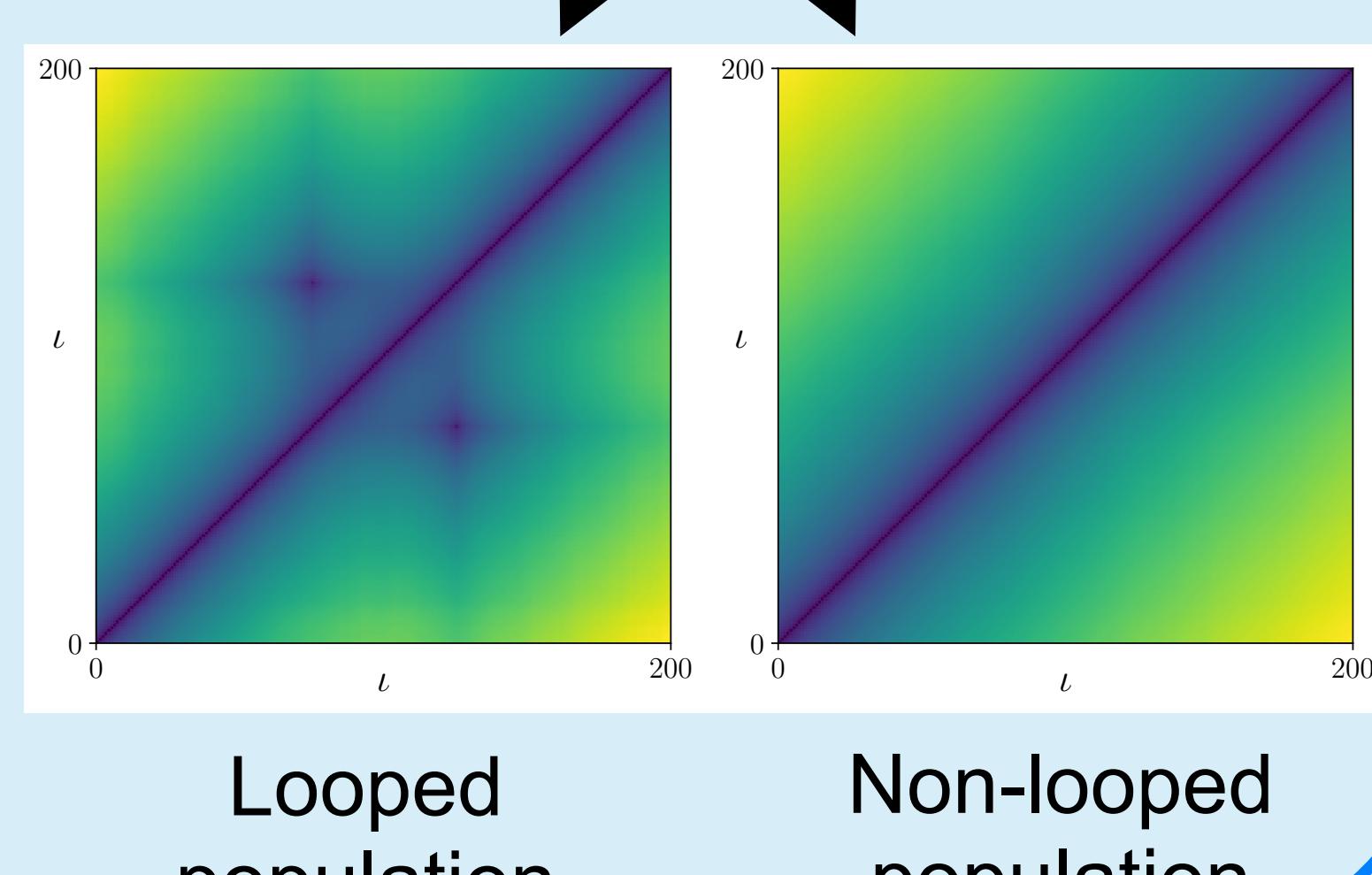
Mix of loops and non-loops



Neural network

Loops

Non-loops



Looped population

Non-looped population

Experimental data:
Bintu et al. 2018[1]

Method:
Sequential FISH

N: 83

Resolution: 30 kb

Cell line: HCT116

Chr. 21

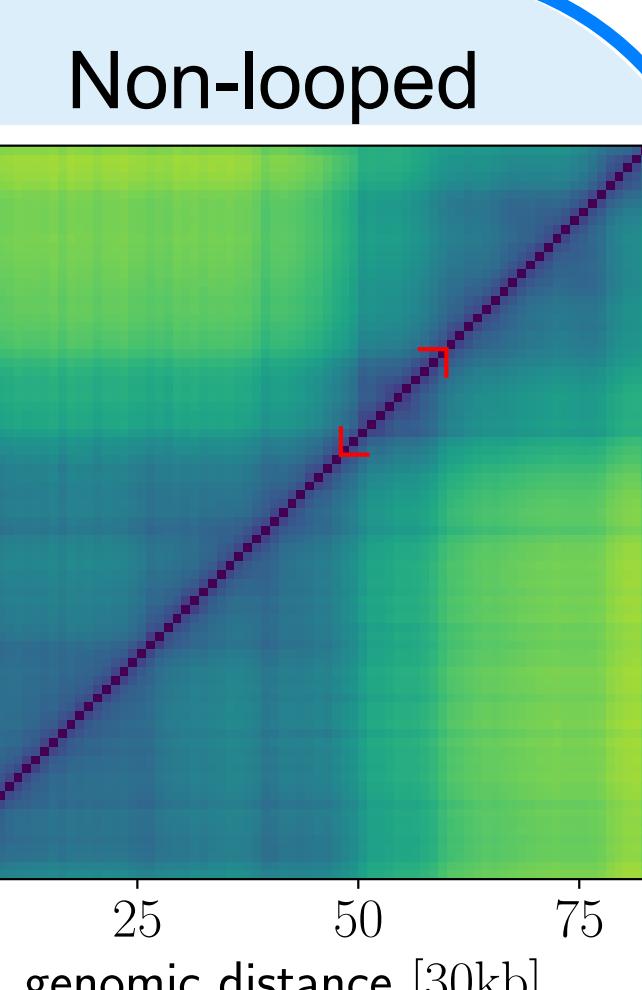
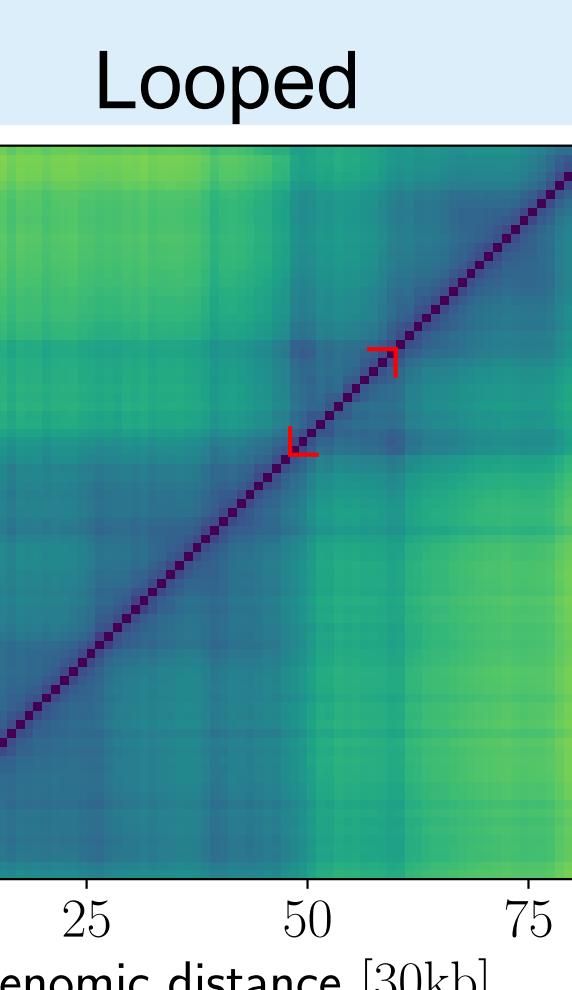
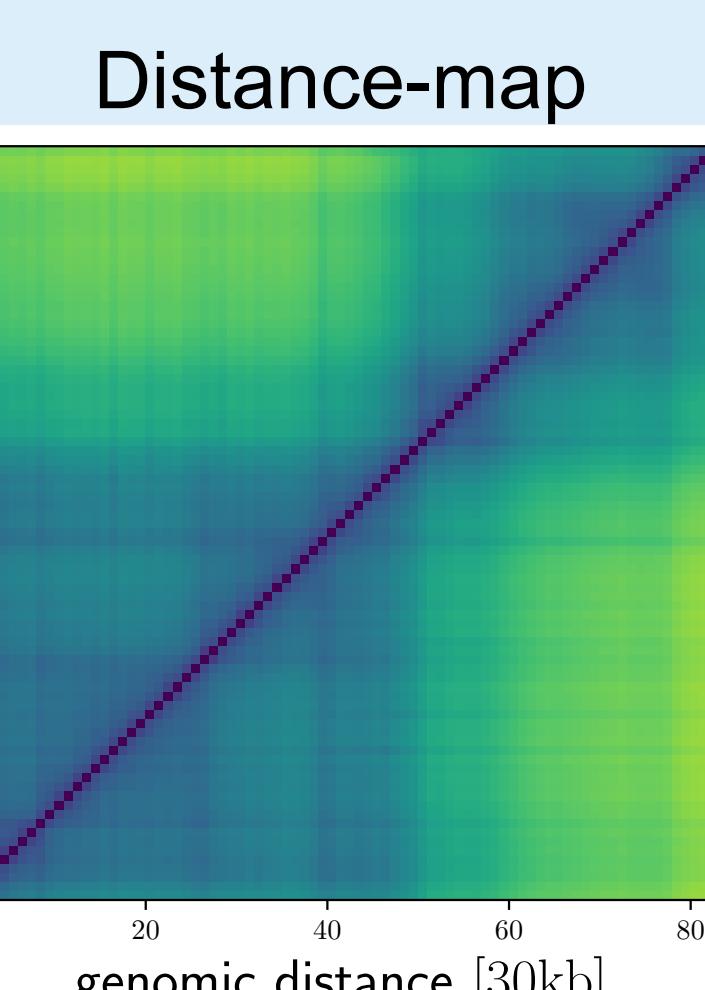
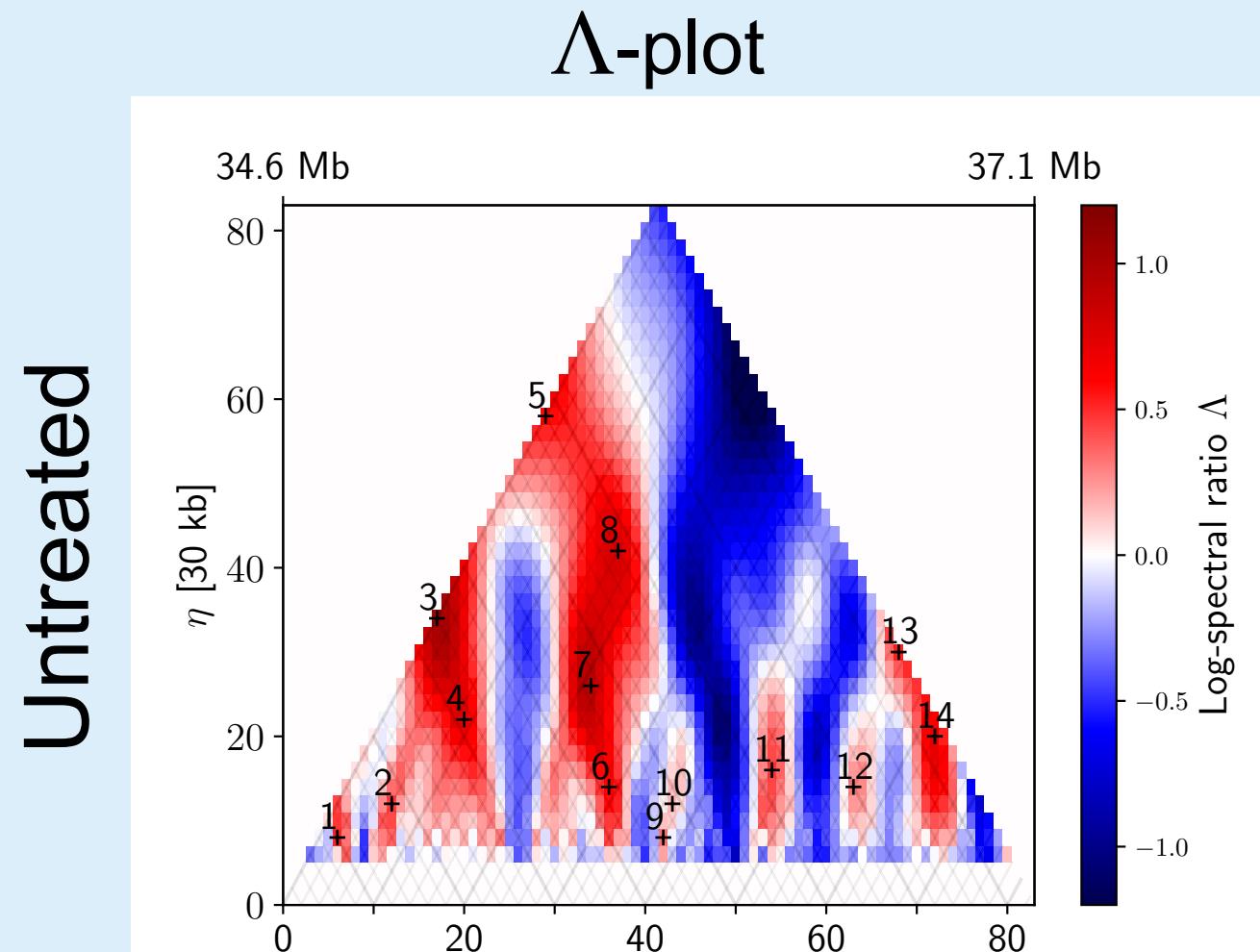
Location: 34.6-37.1 Mb

Two variants:

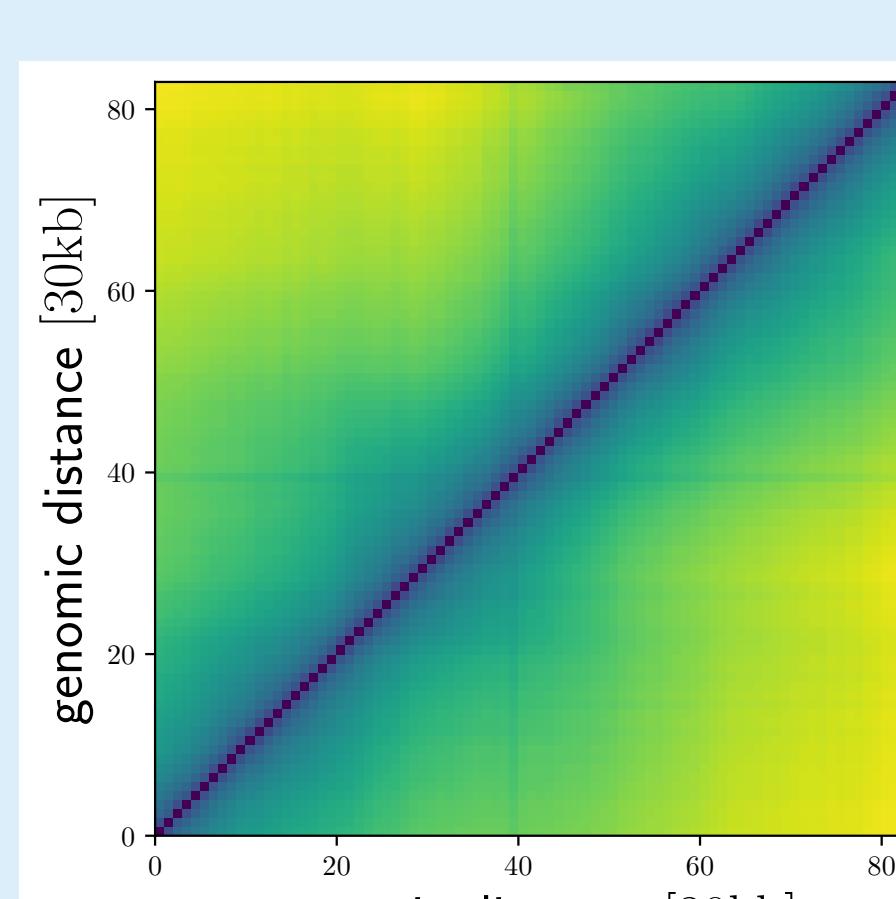
Untreated (11631 samples)

Auxin-treated* (9562 samples)

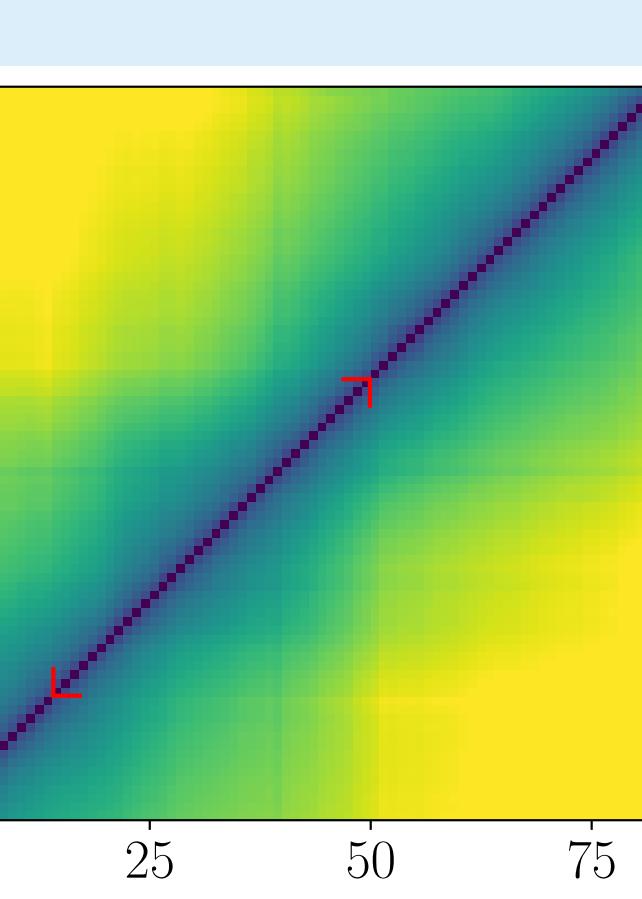
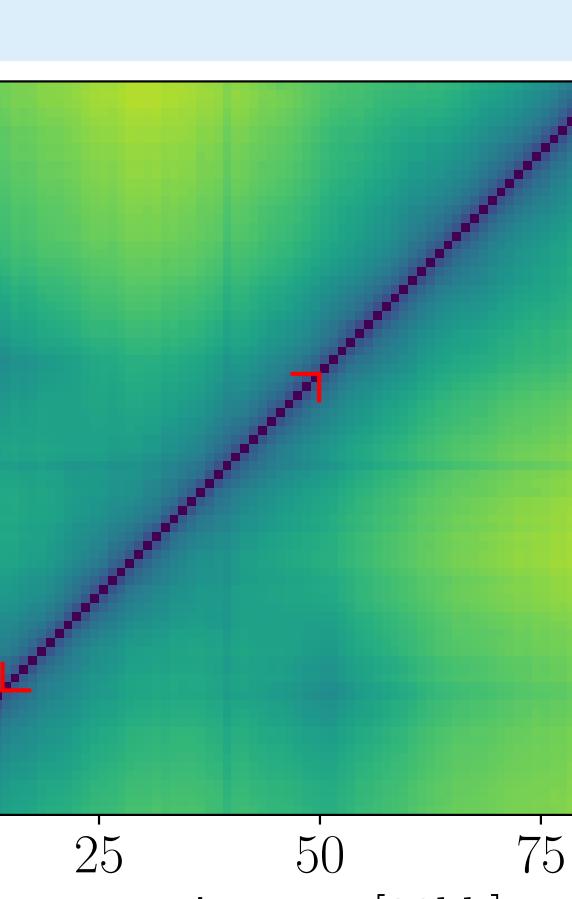
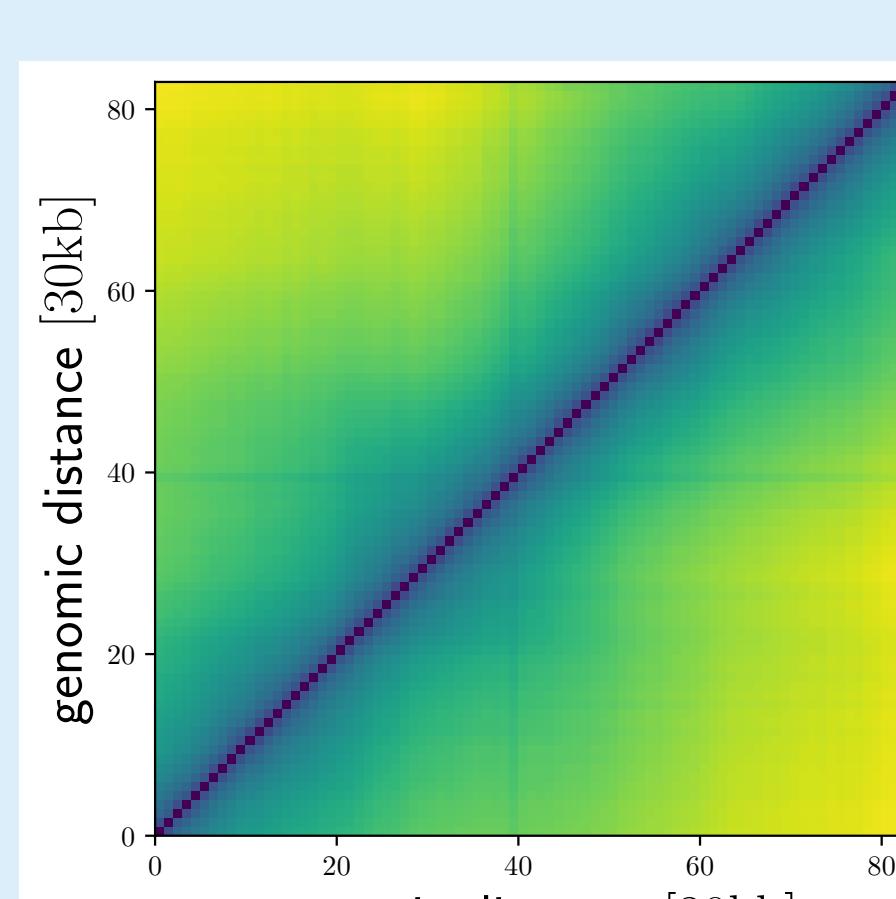
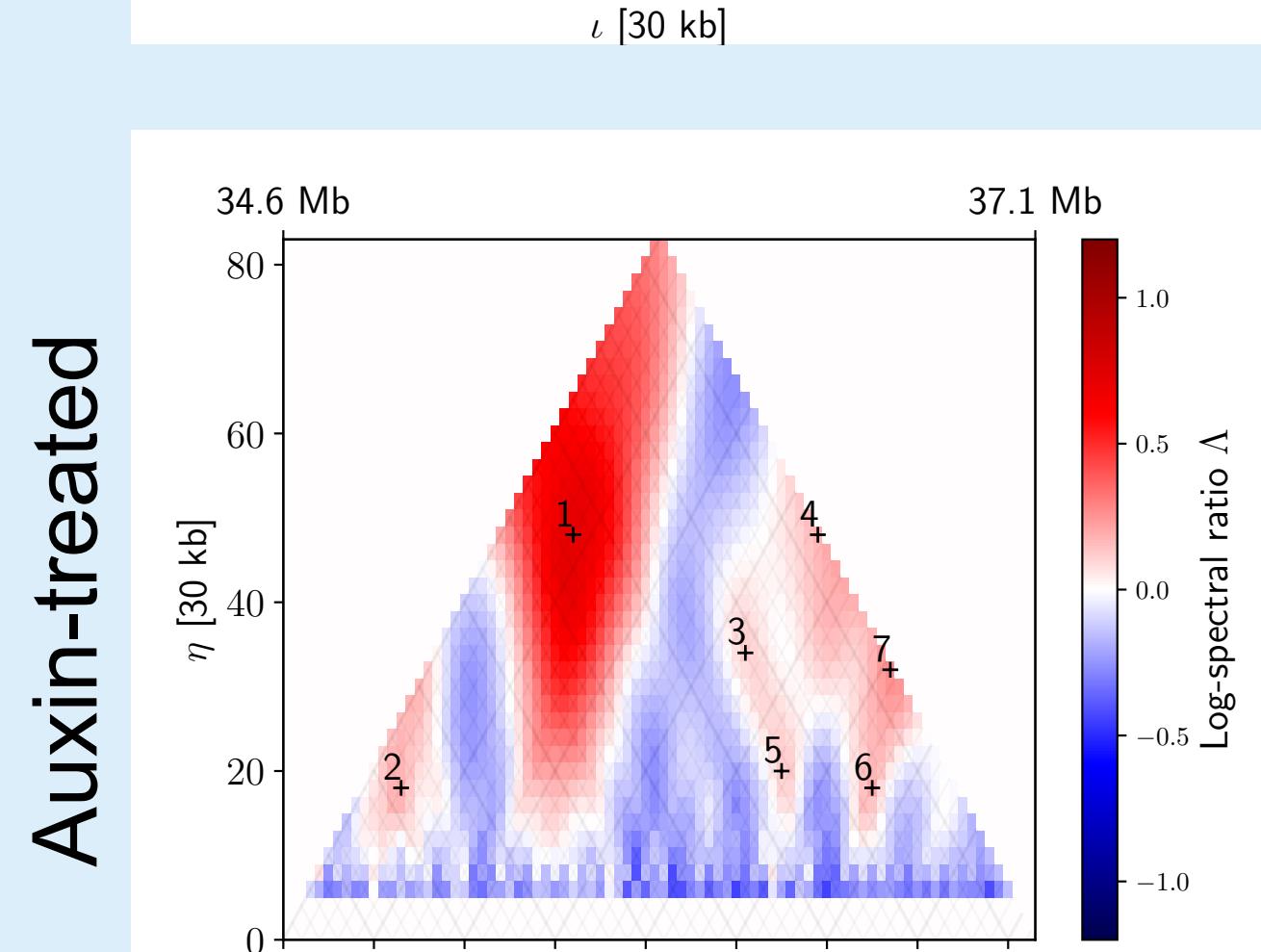
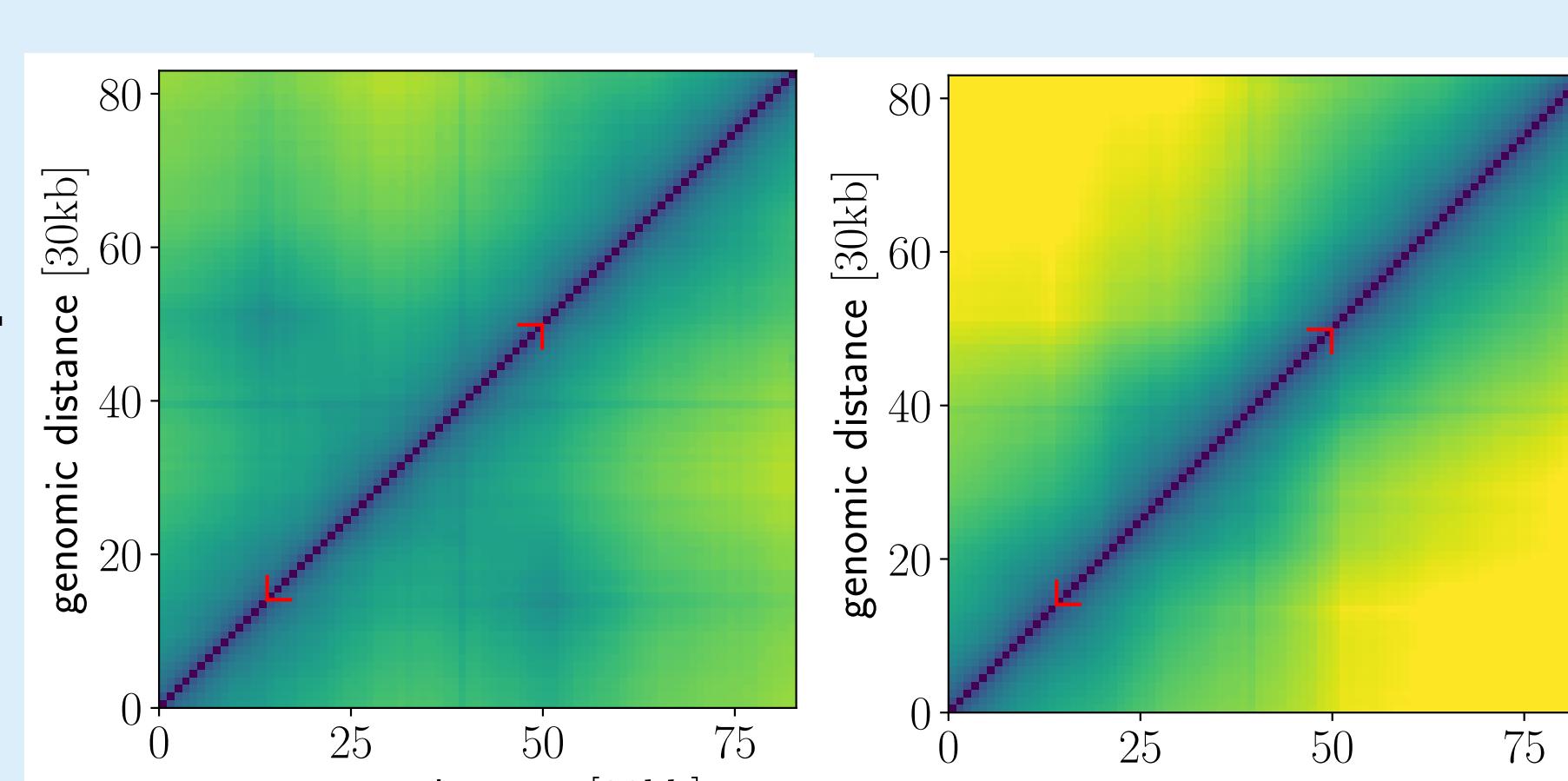
*Auxin causes CTCF depletion



Isolate loop 11

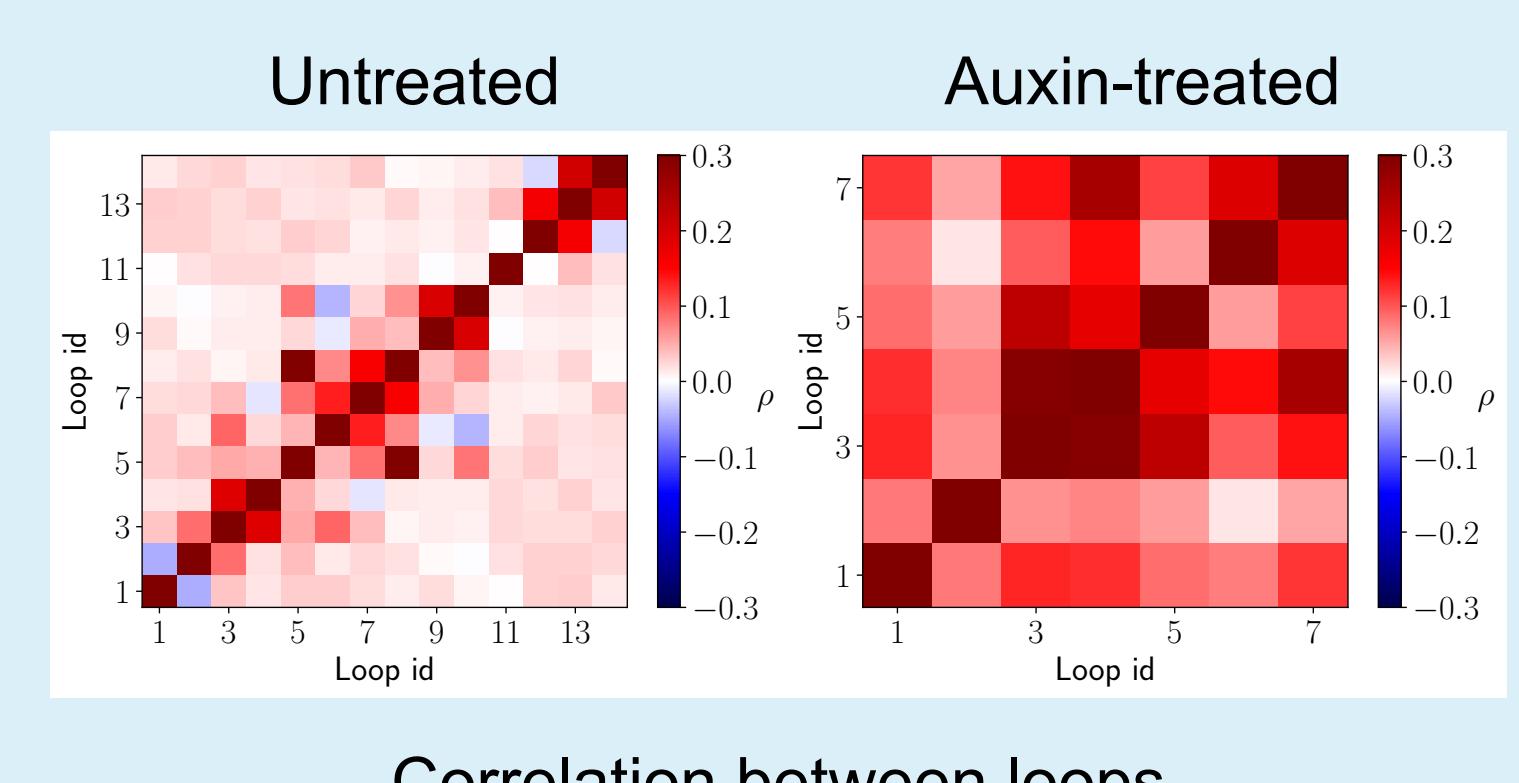
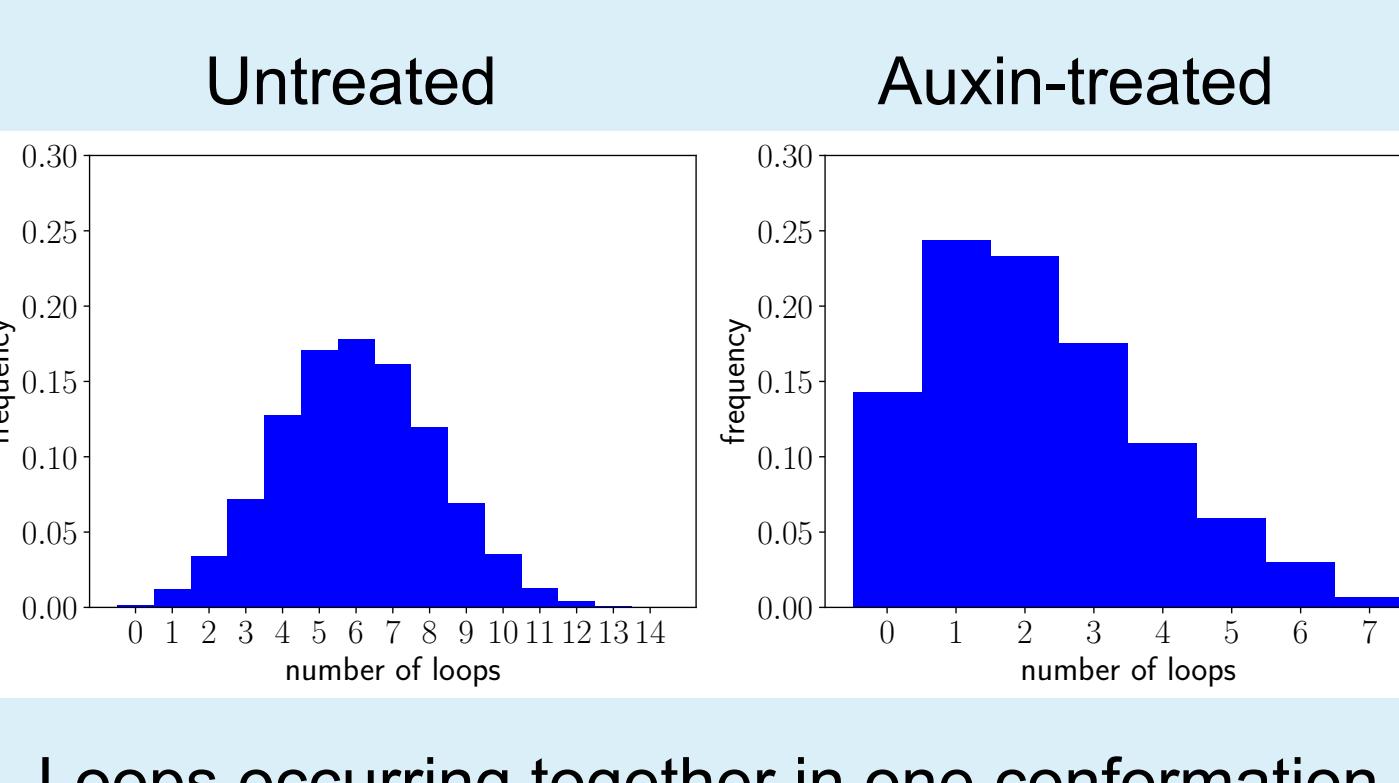
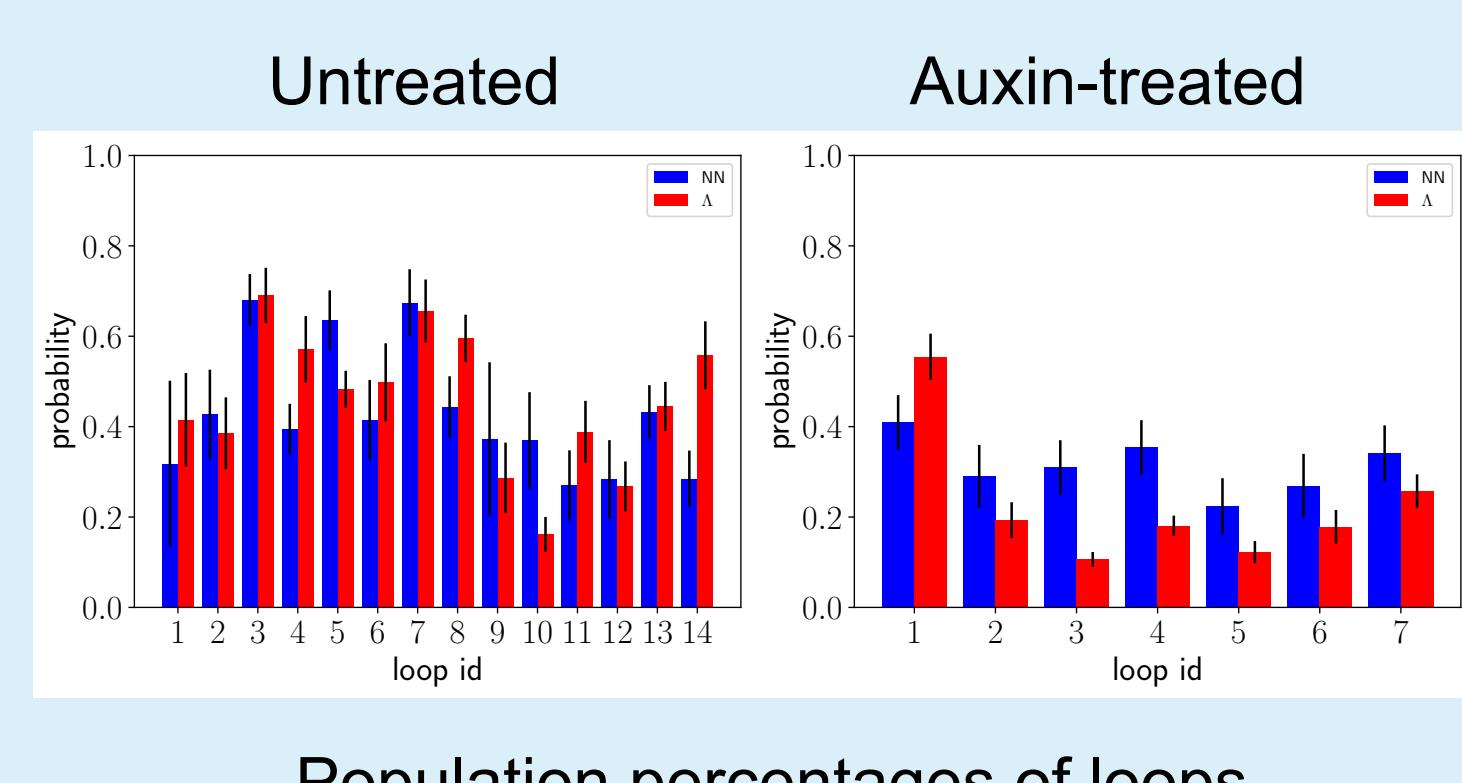


Isolate loop 1



Experimental results

New possibilities



References

[1] Bintu, B. et al. Super-resolution chromatin tracing reveals domains and cooperative interactions in single cells. *Science* **362** (2018).

[2] Földes, T., Lesage, A. & Barbi, M. Assessing the Polymer Coil-Globule State from the Very First Spectral Modes. *Phys. Rev. Lett.* **127**, 277801 (2021).